SHORT COMMUNICATIONS

Clinical Evaluation of a New Antihypertensive Agent: W583 (Mebutamate)

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THE broad variety of antihypertensive drugs presently available testifies that no completely satisfactory agent has yet appeared for the control of hypertension. New products continue to appear with a frequency approaching that of the phenothiazines. In the fall of 1961, a new agent, W583‡ (mebutamate), was made available to us for clinical trial. This material is a close relative of meprobamate (Fig. 1) and could, with equal justification, be called "methylmeprobamate" to emphasize this relationship. As might be expected, a central mode of action is claimed for this drug.[2]

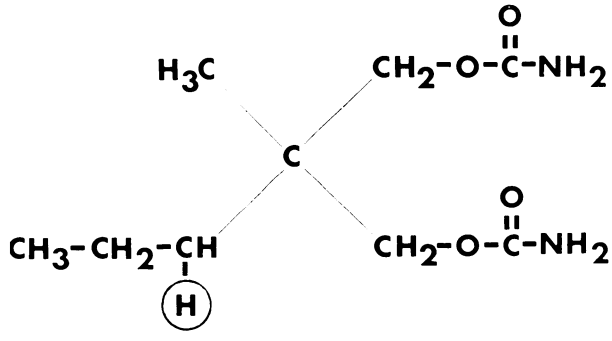

Fig. 1.—Chemical structure of meprobamate. Addition of a methyl group in place of the circled hydrogen ion gives the structure of mebutamate.[1]

Materials and Methods

Nine patients were treated with W583 in a hospital setting after investigation. Eight of these had essential hypertension; the ninth was a 46-year-old man with hypertension secondary to chronic glomerulonephritis. The youngest patient was 46, the oldest 68, and the average age was 56 years. All patients were males.

The doses used ranged from 900 to 2400 mg. per day, given in three or four equal doses. The timing of these doses with relation to meals had no discernible effect on the blood pressure. The blood pressure was taken four times daily with the subject in the standing and lying positions.

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‡The W583 used in this study was supplied through the courtesy of Wallace Laboratories Inc.

ABSTRACT

W583 (Mebutamate) was administered to nine male hypertensive patients in doses up to 2400 mg. per day in an attempt to lower the blood pressure. No other drug was used concurrently. The blood pressure was lowered in two patients only; and the drug was found to be without effect in the remaining seven patients. No postural effect or alteration in pulse was observed. Mild drowsiness was the only effect observed that might be attributable to W583. The duration of treatment varied between three days, in a patient who then developed delirium and a sudden rise in blood pressure, to five months in one other patient. This drug appears to have a very limited place in the treatment of hypertension. Lack of significant demonstrated antihypertensive effect in seven of nine patients suggested that double-blind control studies are not warranted.

Results

In only two of the nine subjects was satisfactory lowering of the blood pressure observed (Table I). In one subject (W.C.), a 51-year-old man whose blood pressure had previously been controlled with 25 mg. of guanethidine a day, we were able to attain satisfactory control with 2400 mg. of W583 per day (Fig. 2). In a second case (C.P.) lowering of the blood pressure from a level of 164/115 to

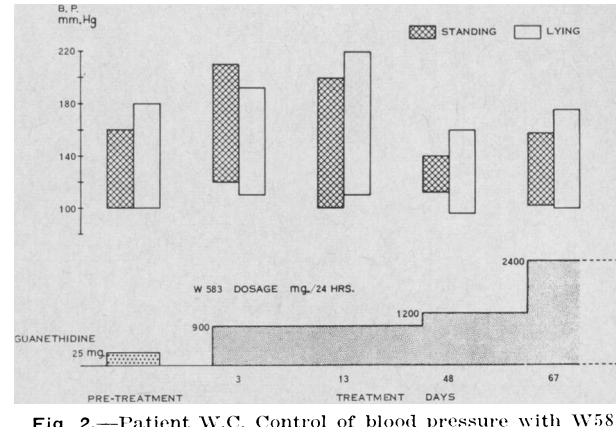

Fig. 2.—Patient W.C. Control of blood pressure with W583 in a patient previously receiving guanethidine, 25 mg. a day.

TABLE I.—CLINICAL DATA FOR EACH PATIENT OF THIS SERIES. THE BLOOD PRESSURE FIGURES REPRESENT THE AVERAGES OF MANY DETERMINATIONS OF THE SUPINE LEVELS, TAKEN ON THE RIGHT ARM.

Patient	*Age*	*Diagnosis*	*Basal blood pressure*	*Blood pressure on W583*	*Dose of W583*	*Duration*	*Side effects*	*Subsequent course*
S.W.	46	Hyperpiesia	160/110 to 150/90	160/95	2400 mg./day	9 days	Nil	No treatment
C.M.P.	49	Hyperpiesia	170/115	160/80 rising to 200/120	900 mg./day	3 months	Nil	No treatment
J.W.C.	52	Hyperpiesia	230/140 falling to 140/100	170/110	1200 mg./day	5 days	Nil	On guanethidine
E.B.	66	Hyperpiesia	220/120	260/150	900 to 1200 mg./day	3 days	Delirium	On guanethidine
W.B.C.	51	Hyperpiesia	210/120	200/110	2400 mg./day	5 months	Nil	Lost to follow-up
L.D.	65	Hyperpiesia	240/130 falling to 200/110	210/110	1200 to 1800 mg./day	10 days	Jaundice (promazine)	On guanethidine
D.A.R.	47	Renal hypertension	150/90	150/100	1200 mg./day	6 days	"Nervous"	No treatment
A.McK.	61	Hyperpiesia	210/110 falling to 170/90	160/95	1200 mg./day	2 months	Nil	On thiazide
H.G.G.	54	Hyperpiesia	160/105	160/100	1200 to 1800 mg./day	9 days	Nil	On guanethidine

160/80 mm. Hg was accomplished with 900 mg. of W583 per day. This excellent control was maintained for a period of three months, when the patient sustained a myocardial infarct, following which his hypertension appeared to be spontaneously "cured".

The remaining seven subjects showed lowering of the systolic blood pressure of less than 10 mm. Hg even with the maximum doses employed, and no discernible differences in their diastolic blood pressures were noted (Fig. 3). In addition, reactions were seen in two patients which may or may not have been related to the drug. One patient (E.B.) developed an acute psychosis after three days of treatment with W583 at a dosage of 1200 mg. per day. At the time this was thought to be a toxic psychosis, but later psychiatric opinion

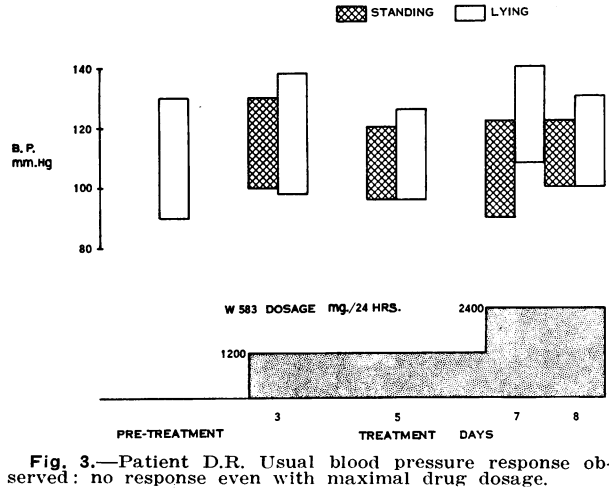

Fig. 3.—Patient D.R. Usual blood pressure response observed: no response even with maximal drug dosage.

expressed the view that this man had had an acute exacerbation of a chronic brain syndrome. Another patient (L.D.) developed clinical jaundice 10 days after beginning the use of W583, but he was concomitantly receiving chlorpromazine, which was considered to be the most likely cause of his jaundice.

DISCUSSION

The pharmacological attack upon hypertension may be central, directed at the so-called vasomotor centre of the brain stem, or peripheral, directed either at the sympathetic nerves or ganglia, or at the arteriolar wall. W583 is said to have a central action similar to its parent compound meprobamate.[2] It is worthy of note that this is the mode of action which we attribute to phenobarbital. Such agents produce their action by a reduction in the cardiac output and a reduction in peripheral resistance. They do not have significant postural effects.

In the two cases in this study in which satisfactory results were obtained with W583, it might be asked whether equally good results might not have been produced with phenobarbital or merely with a period of bed rest. In view of the results with the remaining patients, this possibility must be seriously considered. We did not feel that a double-blind study was warranted with W583 because of the poor results obtained in seven of the nine subjects studied.

All patients in this series complained of some drowsiness, although to some this merely implied the ability to sleep better during the night. The

two side effects noted earlier cannot be attributed to the drug itself, as other adequate explanation is available for each.

We consider that this compound shows little, if any, antihypertensive activity, in accord with the findings reported from Bellevue Hospital, New York, on a larger group of patients.[3] Further investigation of this compound seems unwarranted. Our results suggest that further study using double-blind techniques would add nothing of significant value to the information already obtained. The drug W583 would appear to have little, if any, place in the treatment of hypertension.

SUMMARY

W583 (Mebutamate) was given to nine male hypertensive patients in doses up to 2400 mg. a day, in an attempt to reduce blood pressure. This was successful only in two cases, and was without effect on the blood pressure in seven. The only side effect attributable to the drug was mild drowsiness, which was noted by all patients.

This drug appears to have a very limited application in the treatment of hypertension. Our results suggest that the effects obtained may well have been incidental to sedation, rather than to any specific blood-pressure-lowering effect of this compound.

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A Controlled Trial of Digoxin in the Prevention of the Respiratory Distress Syndrome

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IN 1955, Lendrum[1] suggested that the pulmonary changes occurring in the newborn with respiratory distress could be produced by pulmonary edema resulting from left heart failure. The possibility that cardiac failure may be an important contributory or additive factor has led to the sporadic use of digitalis in the treatment of the respiratory distress syndrome.[2] A double-blind controlled study has been conducted in the premature nursery of the University of Alberta Hospital, Edmonton, to try to establish whether or not the early use of digoxin is effective in preventing or reducing the severity of this syndrome in the newborn infant. The results of this study are presented and the toxic effects of digoxin are discussed.

ABSTRACT

The possibility that cardiac failure may be an important contributory or additive factor has led to the sporadic use of digitalis in the treatment of the respiratory distress syndrome in newborn infants. To assess the value of such medication a double-blind controlled study was conducted on 196 newborn infants, using digoxin and a placebo. As a result of the findings in this study the routine use of digoxin for the prevention of the respiratory distress syndrome is not recommended. The toxic effects of digitalis are outlined.

METHOD

All babies delivered by Cesarean section, babies of diabetic mothers and premature babies (birth weight 5½ lb. and under) born at the University Hospital during part of 1958 and 1959 were included in the first part of the study. On admission to the nursery a sealed envelope, containing a numbered prescription (1-100) and instructions to the nursing staff, was opened. On receipt of the prescription the pharmacy provided, at random, ampoules of identical-appearing solutions, the contents of which were known only to the chief pharmacist. Half of these ampoules contained digoxin (dosage: 0.03 mg./lb. in two divided doses for 24 hours, followed by 0.01 mg./lb./day for three days), and the other half contained glucose and water. These solutions were administered intramuscularly for four days; and the respiratory and pulse rates and retraction scores were recorded at four-hourly intervals. Details of the delivery, Apgar scores, the baby's general condition, treatment, and feeding were noted. Electrocardiograms were recorded in some of the more severe cases and in those with irregular or slow heart beats. Slowing of the pulse to 100/min. or below necessitated examination by the house staff to decide whether or not the injections should be continued. Some of the

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